Assisted reproduction techniques and prenatal diagnosis of Beckwith–Wiedemann spectrum presenting with omphalocele

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We read with interest the article by Johnson and colleagues [1] reporting a huge increase in the odds of artificial reproductive technique (ART) pregnancies among fetuses with Beckwith–Wiedemann spectrum (BWS) presenting with omphalocele. Their valuable report further strengthens the association between ART and imprinting disorders. However, several points deserve to be commented on.

Johnson and colleagues have observed in a large cohort of fetuses with omphalocele that 16 out of 40 (40%) were conceived through ART, compared with 8 out of 261 (3%) without a confirmed molecular diagnosis of BWS. This data led the authors to conclude that the odds of BWS with omphalocele in ART pregnancies are 20-fold that of natural ones, pointing out that it is the highest estimate reported so far besides the first from a prenatal series. We agree that defining the exact increase of BWS risk after ART is burdensome and that previous studies showed remarkable differences in calculated odds/risks, heterogeneous methodologies, and wide confidence intervals in the estimates. Most of these studies were population analyses, case collections, registry studies, or

questionnaire surveys providing indirect estimates by relating the ART rate observed in BWS cohorts to that observed in the general population at the time of the investigation. Johnson and colleagues' estimate, however, is almost twofold the highest and most recent data reported (RR 10.7) [2], which is also the first direct estimate based on the comparison of BWS incidence in ART and non-ART cohorts in a defined time window. We think that the odds the authors provided are barely comparable with data previously reported in literature. The 20-fold estimate refers to the risk of ART in fetuses with BWS + omphalocele in a prenatal setting, not to the odds of ART in BWS, and, moreover, is likely to be largely overestimated due to several factors.

First, the authors assumed a BWS + omphalocele prevalence of 1/17,000, using a BWS prevalence of 1/13,700 [3] and considering omphalocele present in 80% of BWS patients. Actually, more recent BWS prevalence estimates in the general population is higher (nearly 1/10,500) [4], while recent genotype–phenotype studies indicate that only 32% of BWS patients have omphalocele [5–8], thus resulting in an estimate prevalence of BWS + omphalocele of about 1/32,800. Therefore, they calculated the overall risk of BWS + omphalocele following ART of about 1/850 (i.e., 1/17,000 per 20-fold odds); while using more recent data, it would be about 1/1640. However, the latter prevalence is nevertheless overestimated. Indeed, considering that BWS prevalence in ART population is ~1/1100 [2], the maximum risk of BWS + omphalocele following ART can be approximated to be 1/3400 (i.e., 32% of 1/1100). This is to be considered a maximum estimate as omphalocele was reported to be less common in patients with BWS conceived through ART than in those naturally conceived (11–35% [5] [9] vs 32%).

Second, the authors' rough estimate should additionally be lowered taking into account that *CDKN1C* mutation analysis was not performed and that this defect is neither epigenetic nor associated with ART: as pointed out, *CDKN1C* mutation accounts for < 5% of BWS molecular anomalies, but *CDKN1C*-mutated phenotypes have an omphalocele

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incidence more than twofold that reported in the other molecular defects [6]. Hence, *CDKN1C* mutation incidence is expected to be higher than 5% in a cohort of BWSp + omphalocele.

Third, there is a selection bias in the study. Omphalocele is notably associated with centromeric molecular defects (imprinting center 2—IC2—hypomethylation and *CDKN1C* mutation). BWSp cohort pooled data [5] indicate that > 85% of omphalocele occur in patients with IC2 hypomethylation and are consistent with the findings of the authors (36/40). IC2 hypomethylation, however, is also associated with BWSp-ART, representing more than 90% of the molecular anomalies, in contrast to the ~ 50% of non-ART-BWSp [10]. Thus, the authors should expect these two associations to be responsible for an overrepresentation of ART pregnancies in BWSp + omphalocele fetuses.

It is of interest to investigate whether additional BWSp prenatal signs were present and the postnatal phenotype disclosed in the described BWSp cases: this study confirms that a relevant fraction (13–20% [11]) of fetuses with omphalocele have BWSp. This is relevant as it is debated whether testing or not for BWSp infants presenting with isolated omphalocele (European BWSp Consensus [12], recommendation 4).

As a final point, the authors described a case of BWSp-ART with chromosome 11 paternal uniparental disomy (UPD), which occurrence in ART pregnancies is almost anecdotal [2] given that most molecular anomalies in ART-BWSp are related to imprinting defects. While most research on ART-related imprinting disorders hypothesized methylation disturbances arising in the oocyte or in the male gamete [10], UPD likely results from post-fertilization somatic recombination, supporting therefore a pathogenetic role of embryo manipulation. In this respect, further genomic characterization of the region involved in UPD may be crucial in these cases to insight the molecular mechanisms responsible for ART-associated developmental defects.

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